Soz Präventivmed 1993; *38*: 185–189

0303-8408/93/040185-05 $1.50 + 0.20/0

Meta-analysis of environmental and occupational epidemiological studies: A method demonstrated using the carcinogenicity of PCBs as an example

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Meta-analysis, a method for combining the data of several investigations to achieve an overall result, has become an approved technique of research in sociology and psychology. It is increasingly discussed and used for combining the results of controlled clinical trials, but it is not established in environmental and occupational epidemiology. Especially for epidemiological studies it is often difficult to confirm a relationship between exposure and disease because of small prevalences or incidences and long latency periods. In such situations, meta-analysis could be a powerful tool for integrating and combining the results of several studies to reach an overall statement.

One example is the cancerogenity of the polychloride biphenyls (PCBs). More than 20 years ago, a discussion on the noxiousness of PCBs started, and the carcinogenicity of PCBs has been discussed for more than 10 years [1,2,3], but until now, it is not definitely clear whether PCBs can cause cancer in humans or not.

In this article, a concept for meta-analysis – especially of environmental and occupational epidemiological studies – is presented, and demonstrated using the carcinogenicity of PCBs as an example.

Methods

Meta-analysis has become an increasingly popular analytic technique (see [4]), but there are still many different definitions of it in the literature. In this article, the term meta-analysis is used to describe a combination of qualitative and quantitative methods. Qualitative methods are defined as methodological investigations involving the evaluation of several studies using given standards, with the purpose of evaluation and comparison of individual studies. Quantitative methods are defined as using a set of statistical techniques and procedures for combining the results of different studies with the purpose of obtaining a quantitative outcome like a p-value or a risk estimator.

The first step of a meta-analysis is the selection of relevant studies. These studies should be similar with respect to study design, target variables, definition exposure of and possible confounders.

Therefore, to answer the question as to whether there is an association between exposure to PCBs and carcinogenicity in humans, a literature review was performed by using the following selection criteria:

- same study design: SMR-studies (retrospective cohorts)
- comparable observation periods (at least 10 years of exposure between 1940 and 1980)
- comparable cohorts (male workers exposed to PCBs at their working place)
- similar PCB-exposure (exposure to PCBs with 54% or 42% of chlorine).

Several studies were found which examine the consequences of exposure to PCBs, but only 6 of them investigated the relationship between exposure to PCBs at working place and cancer mortality in men [1–3, 5–8]. All these studies define "exposed" as "working at a place with exposure to PCBs"; therefore it was difficult to exclude other exposures. Unfortunately, the results of the individual studies did not, in general, differentiate between the various types of cancer, so that the following analysis cannot do this either.

Results of the selected studies

In all selected studies cancer mortality of the workers (nearly all of them from capacitor plants) was compared with the cancer mortality of a national population.

The results of the studies (n, n_{obs} and n_{exp}) were used for re-analysis using the exact Poisson test (see [9]), exact confidence intervals and exact confidence curves (see [11]).

A summary of the re-analysis is given in table 1.

Concept and results of a meta-analysis

1. Fisher-aggregation of the individual p-values p_i (see [10])

The purpose of the Fisher-aggregation of the exact p-values of the Poisson test is to get a first impression of the relationship between exposure to PCB and cancer mortality.

The hypotheses tested are

$$H_0: \cap (H_0)_i \quad \text{vs} \quad H_1: \cup (H_1)_i,$$

with the test statistic

$$-2 \cdot \sum_{i=1}^{k} \log(p_i) \approx \text{Chi}^2(2k).$$

Tab. 1. Results of re-analysis.

	Study 1	Study 2	Study 3	Study 4	Study 5	Study 6
year of publication	1976/77	1981	1982	1984	1986	1987
number of workers exposed	51	1258	290	153	142	544
reference population used	population of USA	population of USA	population of the city of the plant	population of the region of the plant	population of Sweden	population of Italy
cancer deaths observed (n_{obs})	5	12	8	12	7	14
cancer deaths expected (n_{exp})	0.7	16.53	3.32	4.35	5.39	5.50
exact p-values of a Poisson test with H_0: SMR = 1	0.003	0.245	0.036	0.004	0.523	0.003
$SMR = \frac{n_{obs}}{n_{exp}}$	7.46	0.73	2.41	2.76	1.30	2.55
95% Conf. Int.	(2.37, 16.27)	(0.38, 1.22)	(1.11, 4.66)	(1.46, 4.65)	(0.53, 2.53)	(1.42, 4.14)
Power at $\alpha = 0.05$ for H_1: SMR = 2	–*)	0.92	–*)	–*)	0.52	–*)

*) not relevant, because of significant p-value.

In other words, the null hypothesis of this test is rejected, if in any one of the selected studies there is a deviation (in any direction!) of the risk estimator from the null value 1. In case of rejection, there seems to be an overall deviation from the value 1, so that further investigation is needed. On the other hand, it is not appropriate to do any further investigation, if the resulting p-value is not significant.
Aggregation of the p-values of the 6 selected studies by Fisher leads to a p-value $p < 0.001$.

2. *Estimation of Overall SMRs*

There are different procedures for estimating an overall SMR in the literature (see [10]):

2.1 *Pooling of the data of the individual studies*

If the individual data of the selected studies (n, n_{obs}, n_{exp}) are available, and if the studies are quite similar and comparable, these data can be regarded as coming from only one hypothetical study, and can therefore be pooled.
In this case, an overall SMR can be calculated as $SMR = (\sum n_{obs})/(\sum n_{exp})$.
In this example, these conditions are given, so that pooling the data leads to an SMR of 1.65.

2.2 *Computing weighted sums of the logarithms of the individual SMRs*

If the SMRs of the individual studies are known, an overall SMR can be computed by combining these individual SMRs as

$$SMR = \exp\left(\sum_{i=1}^{k} w_i \cdot \log(SMR_i) / \sum_{i=1}^{k} w_i\right)$$

with weights w_i, $1 \le i \le k$.

There are 2 different methods of weighting:

2.2.1 *Weighting by precision* (see [10])

In this case, the individual SMRs are weighted by the reciprocal values of their variances:

$$w_i = [\mathrm{Var}(\log SMR_i)]^{-1}, \text{ and } 1 \le i \le k$$

The advantage of this kind of weighting is that SMRs from studies with small sample sizes only contribute a little to the overall SMR.
It this example, weighting by precision leads to an overall SMR of 2.01.

2.2.2 *Weighting by homogeneity* (see [11,12])

Here, the individual SMRs are weighted by a modification of the reciprocal values of their variances, which takes into account their deviation from homogeneity. This deviation can be calculated by using the heterogeneity statistic Q which is given below:

$$w_i^* = [\mathrm{Var}(\log SMR_i) + \tau^2]^{-1}, \quad 1 \le i \le k.$$

with

$$\tau^2 = \max\{0, [(Q - (k-1))/(\sum w_i - (\sum w_i^2)/(\sum w_i))]\}$$

and the homogeneity statistic

$$Q = \sum w_i \cdot [\log(SMR_i) - SMR]^2 \quad \text{and}$$

$$SMR = \exp(\sum w_i \cdot \log(SMR_i)/\sum w_i).$$

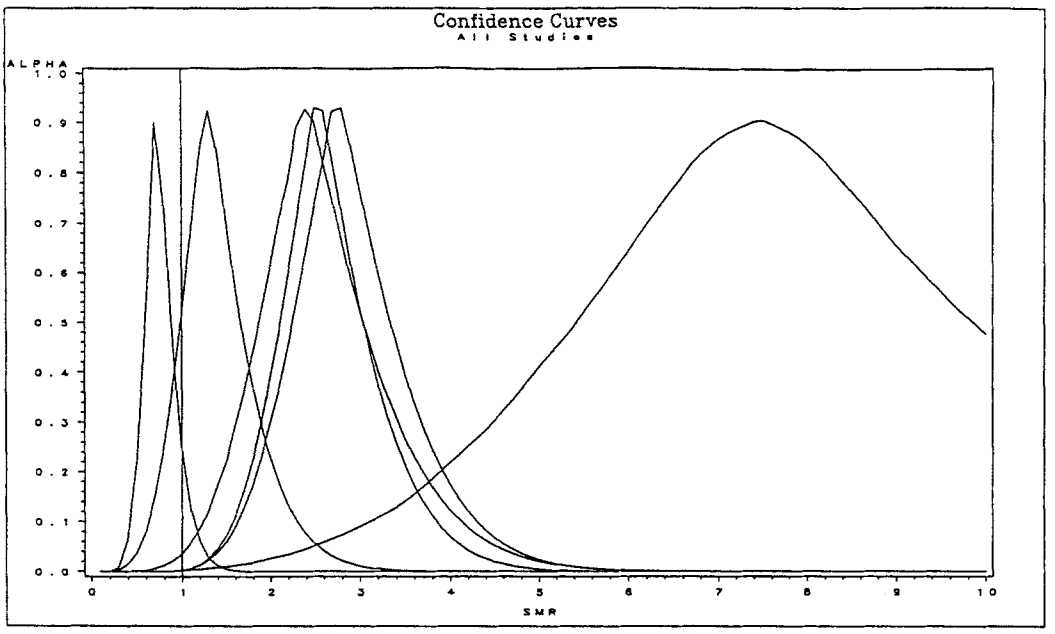

Fig. 1. Confidence curves of the individual SMRs.

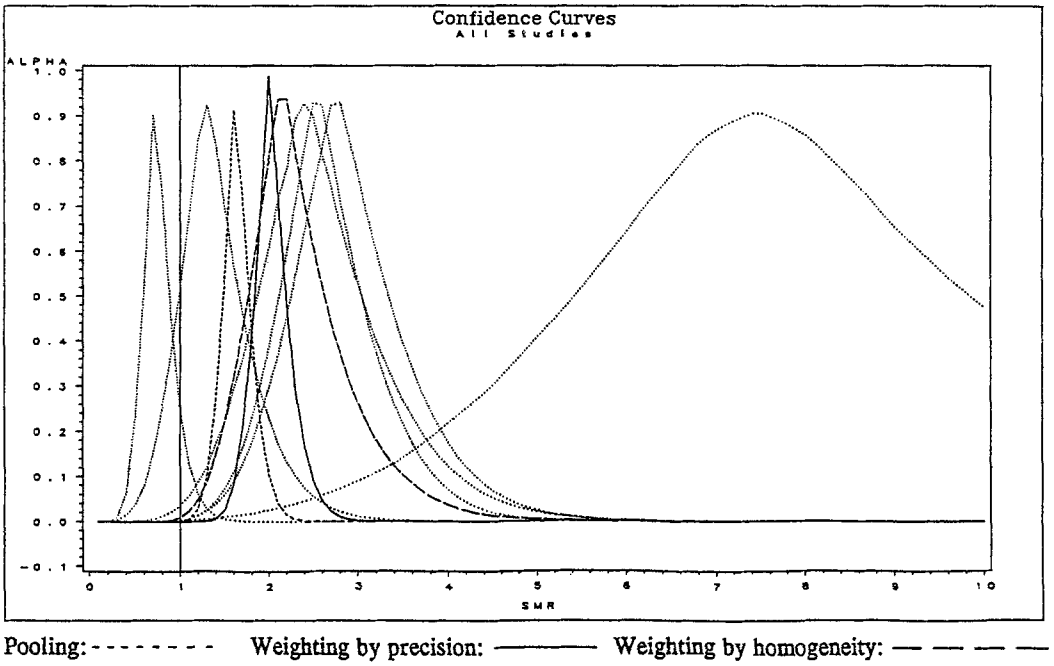

Fig. 2. Combination of the confidence curves of the individual SMRs and the 3 overall SMRs.

These weights are larger than the weights of the precision weighting and therefore lead to larger confidence intervals and curves.
Using this kind of weighting results in an overall SMR of 2.15.

3. Confidence Intervals and Confidence Curves

Corresponding to the different ways of estimation there are different methods for computing confidence intervals and confidence curves. Exact confidence intervals and curves can be calculated for the pooled SMR (see[9,12] and approximative ones for the weighted SMRs as

$$\mathrm{SMR} \cdot \exp\left[\pm z_{1-\alpha/2} \cdot \sqrt{\mathrm{Var}\,(\log \mathrm{SMR})}\right].$$

The results for this example are illustrated in the figures 1 and 2 which are given below.

Discussion

Reviewing the literature for cohort studies investigating the relationship of exposure to PCBs at

work and cancer mortality in men, several epidemiological studies were found, but only six of them were comparable with respect to study design, observation periods, definition of cohorts and exposure.
A re-analysis of these studies was performed using exact statistical methods and computing confidence intervals and confidence curves.
Looking at the confidence curves of the SMRs (see figure 1) a large variation in their results can be seen, so that it is quite difficult to postulate on overall statement.
In such a situation, meta-analysis is an appropriate technique for obtaining overall results.
Conduction of a meta-analysis according to the concept presented above led to various results:

- Aggregation of the individual p-values according to Fisher led to a significant p-value ($\alpha = 0.05$). It is worth mentioning that the Fisher-aggregation is quite conservative and detects deviations from the null hypothesis in any direction. Therefore, a significant result here is hint of something which needs further investigation.
  Using one-sided test procedures in this context is no way out. It is better to consider the studies selected very carefully to determine whether they really share a common effect.
- Three different point estimators for the overall SMR were calculated which are all appropriate in this example. They were quite similar, so that an overall effect of about 2 can be postulated with a better confirmation.
- Computation of confidence curves for these estimators (figure 2) showed that they are all located considerably above the null value 1. Particularly, all 95% confidence intervals do not contain the null value 1.

Summarizing these results, there seems to be a positive association between exposure to PCB at work and cancer mortality in men, which needs further investigation.

Summary

A method for a meta-analysis of several environmental or occupational epidemiological studies with small prevalences and/or incidences and long latency periods is presented. A combination of statistical evaluations of small prevalences should be done in the following way: (1) selecting relevant and comparable studies, (2) computing exact p-values of Poisson tests and aggregating them by Fisher's method, (3) estimating overall relative risks (or SMRs) by pooling the data of the individual studies and by using weighted sums of the logarithms of the individual risks, and (4) calculating confidence intervals and confidence curves for the overall risks. An example illustrates this technique by investigating the association of exposure to polychlorinated biphenyls (PCBs) at work and cancer mortality in men.

Résumé

Méta-analyse des études épidémiologiques en médecine de l'environnement: Un exemple à propos de la carcinogénicité du PCB
Une méta-analyse des études épidémiologiques d'environnement et d'occupation, charactérisée par des prévalences et des incidences petites et des périodes de latence très grandes, est présentée. La combinaison des études est recommandée de la façon suivante: 1) sélection des études pertinentes et comparables, 2) calcul des valeurs exactes d'un test de Poisson et aggrégation par la méthode de Fisher, 3) estimation des risques relatifs ou des SMRs par combinaison des observations des études individuelles et de calculation des sommes de logarithmes d'estimations de risques d'études individuelles et 4) calcul des intervalles et des courbes de confiance pour les estimations générales. Un exemple d'application de cette méthode est utilisé pour la recherche d'une association entre l'exposition aux PCBs et la mortalité par cancer chez les hommes.

Zusammenfassung

Meta-Analyse umwelt- und arbeitsplatzepidemiologische Studien: Zusammenhang zwischen PCB-Exposition und Krebsmortalität
Umwelt- und arbeitsplatzepidemiologische Studien liefern aufgrund kleiner Prävalenzen und Inzidenzen und langer Latenzzeiten oft keine eindeutigen Aussagen zum interessierenden Risiko. In solchen Situationen bieten sich Meta-Analysen an. Die Durchführung einer Meta-Analyse epidemiologischer Studien sollte wie folgt geschehen: (1) Auswahl relevanter und vergleichbarer Studien, (2) Berechnung exakter Poisson-Test-p-Werte und deren Aggregation nach Fisher, (3) Ermittlung von Gesamtrisikoschätzern für Relative Risiken oder SMRs durch Poolen der Daten der Einzelstudien und Kalkulation von gewichteten Summen der Logarithmen der Einzelrisikoschätzer und insbesondere (4) Bestimmung von Konfidenzintervallen und Konfidenzkurven für die Gesamtrisikoschätzer. Dieses Verfahren wird anhand der Durchführung einer Meta-Analyse zum Zusammenhang zwischen einer PCB-Exposition am Arbeitsplatz und der Krebsmortalität bei Männern demonstriert.

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